INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 98/03872

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q1/68 A61K31/70 A61K39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 06952 A (NEW YORK SOCIETY FOR THE RUPTU) 7 March 1996 see the whole document	1-11, 13-17
X	WO 97 46715 A (NEW YORK SOCIETY FOR THE RUPTU) 11 December 1997 see the whole document	1-11, 13-17
X	WO 95 05481 A (ISIS INNOVATIONS LTD) 23 February 1995 see page 10, line 23 - page 12, line 1; claims 1-3	1-8,17
X	WO 97 08338 A (ISIS INNOVATIONS LTD ;COOKSON WILLIAM OSMOND CHARLES (GB); HILL MI) 6 March 1997 see claims 1-19	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 1999	27/04/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Osborne, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I. national Application No
PCT/GB 98/03872

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	RASCU A ET AL: "Clinical relevance of Fc. gamma. receptor" ANN. NEW YORK ACAD. SCI., vol. 815, 1977, pages 282-95, XP002069827 see page 289 - page 292 ---	1-17
X	WU J ET AL: " NOVEL POLYMORPHISM OF FC gamma RAIIIA (CD16) alters receptor function and predisposes to autoimmune disease" JOURNAL OF CLINICAL INVESTIGATION, vol. 100, no. 5, September 1997, pages 1059-70, XP002069828 see the whole document ---	1-11,16, 17
X	WO 94 29351 A (CELLTECH LTD ;MORGAN SUSAN ADRIENNE (GB); EMTAGE JOHN SPENCER (GB)) 22 December 1994 see example 1 -----	7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/03872

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 2,4 (wholly) and 6,8-14(partially) is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
–

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
PCT/GB 98/03872

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9606952 A	07-03-1996	US 5830652 A	03-11-1998
		CA 2198780 A	07-03-1996
		EP 0784702 A	23-07-1997
		JP 10504965 T	19-05-1998
WO 9746715 A	11-12-1997	NONE	
WO 9505481 A	23-02-1995	NONE	
WO 9708338 A	06-03-1997	AU 6830696 A	19-03-1997
		EP 0842299 A	20-05-1998
WO 9429351 A	22-12-1994	AU 691811 B	28-05-1998
		AU 6934194 A	03-01-1995
		AU 694926 B	06-08-1998
		AU 6934294 A	03-01-1995
		CA 2163344 A	22-12-1994
		CA 2163345 A	22-12-1994
		EP 0714409 A	05-06-1996
		EP 0715653 A	12-06-1996
		WO 9429451 A	22-12-1994
		JP 8511420 T	03-12-1996
		JP 8511421 T	03-12-1996

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
COCKBAIN, Julian
FRANK B. DEHN & CO.
179 Queen Victoria Street
London EC4V 4EL
GRANDE BRETAGNE

FILE 67440|004
13 OCT 1999
AIN: 60

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	11.10.99
Applicant's or agent's file reference: 44.67440/004	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/03872	22/12/1998	22/12/1997

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
STIFTELSEN UNIVERSITETSFORSKNING BERGEN .. et al

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 22/04/2000.

DUE DATE NOTED
11/12/99

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Herrero, M

Formalities officer (incl. extension of time limits)
Digiusto, M
Telephone No. +49 89 2399 8162

Form PCT/IPEA/408 (cover sheet) (January 1994)

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-21 as originally filed

Claims, No.:

1-15 as originally filed

Drawings, sheets:

1/1 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 2, 4, 6, 7, 8-14 (part),

because:

☒ the said international application, or the said claims Nos. 2, 4, 6, 7, 8-14(part) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	7, 8-14(part), 15
Inventive step (IS)	Claims	1-8, 9-14(part), 15
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION III

Claims 2, 4, 6, 7 and 8-14(part) relate to medical uses considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). For the assessment of the present Claims 2, 4, 6, 7 and 8-14(part) on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 Reference is made to the following documents:

D1: WO 96/06952

D2: WO 97/46715

D3: WO 95/05481

D4: WO 97/08338

2.2 Novelty and inventive step (Art. 33(2) and (3) PCT)

The present application does not satisfy the criteria set forth in Article 33(2) and (3) PCT because,

a) the subject-matter of Claims 7, 8-14(part) and 15 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT)

b) the subject-matter of Claims 1-8, 9-14(part) and 15 does not involve an inventive step (Rule 65(1)(2) PCT).

It would appear that a number of primers, allele-specific oligonucleotides and oligonucleotide hybridization probes falling under the generic denomination "FcR allele-specific binder" have been previously employed for the purposes of diagnostic and/or prognosis.

In this regard attention is drawn to the relevant teachings of D1, in particular the described use therein of two oligonucleotides specific for the FcγRIIA HR and LR alleles in Examples 4 and 5 and of several oligonucleotides specific for the FcγRIIIB NA1 and NA2 alleles in Example 6 on pages 16-17 (see also Claims 1, 4 and 11). Likewise, attention is drawn in D2 to the description of related uses of FcγRIIIA allele-specific oligonucleotides in page 14, lines 15-24 and page 15; Example 2 on pages 26-27 and Claims 9-11.

Furthermore, see in D3 Claims 1-4 and the oligonucleotides corresponding to SEQ ID Nos 3 and 4 on page 4, lines 17-36 and SEQ ID Nos 10 and 11 on page 14, lines 1-12 , all of them FcERI-ß allele-specific. In connection with diagnostic applications of the analysis of FcERI-ß polymorphisms see also D4, e.g. Claim 13.

In view of the above, D1, D2, D3 and D4 seemingly anticipate and/or render obvious the generically formulated independent Claims 7 and 15. The first medical use of a "FcR allele-binder" according to Claim 8 (part) and Claims 9-14(part) would in particular appear not to satisfy the criteria set forth by Art. 33(2) and (3) PCT vis-à-vis D1 (Claims 8-14) and D2 (Claim 8).

Moreover, due to the fact that diseases as e.g. myasthenia gravis or Addison's disease have unavoidably to be considered as autoimmune diseases, Claims 1-5 referring to a "Fc receptor" lacking further characterization, appended Claim 6

which relies on the use of an indefinite "FcR allele-specific binder" and dependent Claims 8 and 9 [as long as these latter (a) rely either on the method of Claims 1-4, the diagnostic assay of Claim 5 or the second medical use of Claim 6 and (b) respectively refer to a generic Fcγ receptor (Claim 8) or to FcγRIIA and/or FcγRIIIB (Claim 9)] would appear in the present technical context to be rendered obvious, at least in part, by the available prior art, see e.g. D1 (cf Claim 1),.

2.3 Notwithstanding the foregoing, it is noted that the present application discloses, apparently for the first time, certain FcγRIIA and FcγRIIIB specific genotypes that either are associated with or are indicative of benign prognosis *versus* non-benign prognosis in a number of particular diseases (see page 9, lines 35-37 bridging over page 10, lines 1-13 and Examples 1 to 6). Thus, in the light of the supporting description, present Claims 10-14 (insofar as they rely on the methods of Claim 1-4 or the diagnostic assay of Claim 5) would appear to relate to novel and inventive subject-matter (Art. 33(2) and (3) PCT).

2.4 The applicant is requested to file new claims which take account of the above comments (see also Section VIII below).

Concerning a possible reformulation of Claim 15 it should be kept in mind that, irrespective of their intended use, any claimed kit of parts has to meet *per se* the novelty and inventive step requirements of Art. 33(2) and (3) PCT.

2.5 The applicant is requested to file amendments by way of replacement pages in the manner stipulated by Rule 66.8(a) PCT. In particular, fair copies of the amendments should be filed preferably in triplicate.

Moreover, the applicant's attention is drawn to the fact that, as a consequence of Rule 66.8(a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.

2.6 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern

amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

2.7 Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply rather than be incorporated into the application, Article 34(2)(b) PCT.

SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 is not mentioned in the description, nor are these documents identified therein.

2. The terms "QIAamp" (page 11, lines 21 and 24), "Eppendorf" (page 11, line 30) and "Medprobe" (page 12, line 3) appear to be registered trade marks, but have not been acknowledged as such.

SECTION VIII

1. The generic expression FcR "allele-specific binder" used in Claims 6-15 has no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, e.g. which is the nature/composition of the intended "binder"?, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

In order to overcome this deficiency the nature of the "allele-specific binder" of interest should be more accurately defined as, e.g. allele-specific primers or allele-specific binder (oligonucleotide) sequences (see supporting description on page 8, lines 32-37.

2. For the sake of clarity Claims 12, 13 and 14 should better more precisely refer to FcγRIIIB NA1/NA1 (Claim 12), FcγRIIA H/H (Claims 12 and 14) and FcγRIIIB NA2/NA2 (Claim 13).

3. The following expressions appear to contain clerical mistakes:

"cardiocascular": page 2, lines 13 and 26; page 3, line 2; page 4, line 36; page 6, line 37; page 7, line 24 and Claims 1, 2, 3 and 5.

"... after 45 minutes of 70 volts": page 13, line 31

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

COCKBAIN, Julian
FRANK B. DEHN & CO.
179 Queen Victoria Street
London EC4V 4EL
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	01.03.00
Applicant's or agent's file reference 44.67440/004	**IMPORTANT NOTIFICATION**
International application No. PCT/GB98/03872	International filing date *(day/month/year)* 22/12/1998
Priority date *(day/month/year)* 22/12/1997	
Applicant STIFTELSEN UNIVERSITETSFORSKNING BERGEN .. et al	

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/ European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Digiusto, M Tel.+49 89 2399-8162

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
44.67440/004		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/03872	22/12/1998	22/12/1997
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant STIFTELSEN UNIVERSITETSFORSKNING BERGEN .. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/07/1999	01.03.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herrero, M Telephone No. +49 89 2399 8542

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/03872

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1,5,8-12,14-21	as originally filed			
2-4,6,7,13	as received on	08/02/2000	with letter of	04/02/2000

Claims, No.:

1-14	as received on	08/02/2000	with letter of	04/02/2000

Drawings, sheets:

1/1	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 2, 4, 6, 7-13(part) with respect to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 2, 4, 6, 7-13(part) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-13
	No:	Claims 14
Inventive step (IS)	Yes:	Claims 9-13
	No:	Claims 1-8, 14
Industrial applicability (IA)	Yes:	Claims 1, 3, 5, 14
	No:	Claims 2, 4, 6, 7-13(part). See Section III

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION I

4. Additional observations

Apparently by mistake the newly filed Claims 1 to 14 contain two consecutive claims numerated as Claim 9. Nevertheless, the following sections will actually refer to (the intended) Claim 8, i.e. the newly filed claim derived from Claim 9 as originally filed.

SECTION III

Claims 2, 4, 6 and 7-13(part) relate to medical uses considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). For the assessment of the present Claims 2, 4, 6 and 7-13(part) on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 The following documents have been considered for the purposes of this report:

D1: WO 96/06952
D2: WO 97/46715
D3: WO 95/05481
D4: WO 97/08338

2.2 Novelty and inventive step (Art. 33(2) and (3) PCT)

The arguments set forth by the Applicants to substantiate the subject-matter encompassed by the newly filed Claims 1 to 14 as novel and non-obvious over the cited prior art D1-D4 have been taken into account (cf Applicants' letter of 04.02.2000 in reply to the written opinion dated 11.10.99). However, the present IPEA still considers that the present application does not satisfy the criteria set forth in Article 33(2) and (3) PCT because,

a) the subject-matter of Claim 14 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT)

b) the subject-matter of Claims 1-8 and 14 does not involve an inventive step (Rule 65(1)(2) PCT).

A number of primers, allele-specific oligonucleotides and oligonucleotide hybridization probes falling under the generic denomination "FcR allele-specific binder" have been previously employed for the purposes of diagnostic and/or prognosis.

In this regard attention is drawn to the relevant teachings of D1, in particular the described use therein of two oligonucleotides specific for the FcγRIIA HR and LR alleles in Examples 4 and 5 and of several oligonucleotides specific for the FcγRIIIB NA1 and NA2 alleles in Example 6 on pages 16-17 (see also Claims 1, 4 and 11). Likewise, attention is drawn in D2 to the description of related uses of FcγRIIIA allele-specific oligonucleotides in page 14, lines 15-24 and page 15; Example 2 on pages 26-27 and Claims 9-11.

Furthermore, see in D3 Claims 1-4 and the oligonucleotides corresponding to SEQ ID Nos 3 and 4 on page 4, lines 17-36 and to SEQ ID Nos 10 and 11 on page 14, lines 1-12, all of them FcERI-ß allele-specific. In connection with diagnostic applications of the analysis of FcERI-ß polymorphisms see also D4, e.g. Claim 13.

In view of the above the disclosures of D1, D2, D3 and D4 seemingly anticipate and/or render obvious the broadly formulated "prognostic kit comprising at least one FcR allele-specific binder" according to independent Claim 14.

In this regard the attention of the Applicants is drawn to the fact that the "instructions for the performance of a method of prognosis, prophylaxis or therapy" referred to in Claim 14 is not regarded as a technical feature and cannot be used for establishing novelty and/or inventive step over the prior art of the hereby claimed prognostic kit (cf PCT Guidelines C-III, 2.1 and Rule 6.3(a) PCT).

It is emphasized that any claimed kit of parts has to meet *per se* the novelty and inventive step requirements of Art. 33(2) and (3) PCT and that a particular intended use (e.g. the uses implied in the methods of disease prognosis according to Claims 1 or 3) would also not limit the scope of the claim to the mentioned use (cf PCT Guidelines III-4.8).

On the other hand, due to the fact that diseases as e.g. myasthenia gravis or Addison's disease have unavoidably to be considered as autoimmune diseases, Claims 1-5 referring to a "Fc receptor" lacking further characterization, the (medical) use according to independent Claim 6 which relies on an indefinite "FcR allele-specific binder" and dependent Claims 7 and 8 [as long as these latter (a) rely either on the methods of Claims 1-4, the diagnostic assay of Claim 5 or the (medical) use of Claim 6 and (b) respectively refer to a generic Fcγ receptor (Claim 7) or to FcγRIIA and/or FcγRIIIB (Claim 8)] would appear in the present technical context to be rendered obvious, at least in part, by the aforementioned relevant teachings of the available prior art, e.g., D1 (cf Claims 1 and 4-11) and D2 (Claims 9-11).

Regarding the above it is pointed out that none of independent Claims 1, 2, 3 and 5 contains all the technical features essential to the solution of the problem to which the invention is addressed. Accordingly the skilled person is not provided in Claims 1, 2, 3 and 5 with the necessary information required to carry out the invention without undue experimentation (see also item 1 of Section VIII below).

2.3 Notwithstanding the foregoing, it is noted that the present application discloses, apparently for the first time, certain FcγRIIA and FcγRIIIB specific genotypes that either are associated with or are indicative of benign prognosis *versus* non-benign prognosis in a number of particular diseases (see page 9, lines 35-37 bridging over page 10, lines 1-13 and Examples 1 to 6). Thus, in the light of the supporting description, present dependent Claims 9-13 would appear to relate to novel and inventive subject-matter (Art. 33(2) and (3) PCT).

SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 is not mentioned in the description, nor are these documents identified therein.

2. The terms "QIAamp" (page 11, lines 21 and 24), "Eppendorf" (page 11, line 30) and "Medprobe" (page 12, line 3) appear to be registered trade marks, but have not been acknowledged as such.

3. As mentioned in Section I above, two consecutive claims have been numerated as Claim 9.

SECTION VIII

1. Independent Claims 1, 2, 3 and 5 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result, i.e. for every selected disease the particular Fcγ RIIA and/or Fcγ RIIIB allelic forms which together or separately are indicative of benign *versus* non-benign prognosis, should have been added.

2. The use in Claims 6 and 14 of the generic expression "FcR allele-specific binder" leaves the reader in doubt as to the meaning of the technical features to which it

refers (e.g. which is the nature/composition of the intended "binder"?) thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

In order to overcome this deficiency the nature of the "allele-specific binder" of interest should have been more accurately defined as, e.g. allele-specific primers or allele-specific binder (oligonucleotide) sequences (see supporting description on page 8, lines 32-37).

3. Claim 4 (2nd and 3rd lines) reads "prophylactally".

and therapeutic or palliative treatment may be given to early (and later) stage disease sufferers.

While there have been suggestions that there may be genetic markers for the progression of certain immune-related diseases, our investigations show that this does not appear in any way to be generally applicable (e.g. for poliomyelitis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, rheumatoid arthritis, etc.). However we have now found that an individual's genotype for Fc receptors provides the basis for such prognostication for multiple sclerosis, myasthenia gravis, diabetes mellitus, cerebrovascular and cardiovascular diseases, atherosclerosis, and Addison's disease, a range of diseases which includes diseases which are not considered to be infection- or immune-related, e.g. in particular atherosclerosis and cardiovascular and cerebrovascular diseases.

Thus viewed from one aspect the invention provides a method of disease prognosis which involves determining the genotype of a human or non-human mammal subject for at least one Fc receptor, preferably an Fcγ receptor, and identifying whether the determined genotype corresponds to a benign or non-benign prognosis for a disease selected from multiple sclerosis, myasthenia gravis, diabetes mellitus, cerebrovascular and cardiovascular diseases, atherosclerosis, and Addison's disease.

By benign and non-benign prognoses, it is meant that the prognoses are more or less benign, e.g. good or not-so-good or bad or worse, etc.

This method may be considered to be one for determination of an indicator which may used by the physician in disease prognosis and, if necessary, the selection of appropriate treatments.

Viewed from a further aspect the invention provides a method of prophylaxis or therapy of a human or non-human mammal subject to combat a disease selected from

multiple sclerosis, myasthenia gravis, diabetes mellitus, cerebrovascular and cardiovascular diseases, atherosclerosis, and Addison's disease, which method comprises determining the genotype of said subject for at least one Fc receptor, identifying whether the determined genotype corresponds to a benign or non-benign prognosis for said disease, and, where said determined genotype corresponds to a non-benign prognosis, carrying out a diagnostic imaging procedure on said subject, carrying out surgical intervention on said subject, or administering a prophylactically or therapeutically effective amount of a material prophylactically or therapeutically effective against said disease to said subject.

By way of example if the prognosis for atherosclerosis giving rise to heart or brain infarct is non-benign, early diagnostic imaging of the patient's vasculature may be recommendable and if stenoses are detected, surgical intervention, e.g. percutaneous transluminal angioplasty (PCTA), may reduce the likelihood of infarction so reducing future healthcare costs and improving the patient's future quality of life. Similarly, a non-benign prognosis according to the present invention, optionally coupled with detection of other risk factors such as high blood cholesterol, high homocysteine, high triglycerides, and high blood pressure may assist an individual to effect life style changes which will reduce the likelihood of development of atherosclerosis or of other cerebrovascular or cardiovascular disease, including the likelihood of infarction. Such changes may include cessation of smoking, change of diet, increase in regular exercise, reduction of stress, etc.

For diabetes mellitus, if the prognosis is non-benign, earlier insulin treatment, implantation of an insulin pump, or earlier pancreas or kidney transplant may prevent or delay onset of serious diabetes effects,

e.g. diabetic retinopathy.

In the case of Type II (non-insulin dependant) diabetes patients, where the prognosis is non-benign, life style changes, weight loss, low-sugar diet and careful monitoring of blood sugar and/or insulin levels and possible early prescription of insulin may delay transition to or severity of Type I diabetes. For Type I patients, a non-benign diagnosis may support earlier insulin treatment, implantation of an insulin pump, etc. as mentioned above.

In the case of multiple sclerosis, a non-benign prognosis may predicate earlier prophylactic or therapeutic treatment, e.g. with interferons or gamma-globulin. Since such drugs are very expensive, the methods of the invention allow a more targetted use of medical and financial resources.

To determine the genotype of an individual for an Fc receptor, it is necessary to obtain a sample of the DNA of that individual. For this it is necessary to use FcR allele-specific binders (e.g. PCR primers or other materials capable of selectively binding to DNA or DNA fragments containing the particular FcR allele).

Accordingly, viewed from a further aspect, the invention provides the use of an FcR allele-specific binder for the manufacture of a composition for use in a method of prognosis, prophylaxis or therapy according to the invention.

Viewed from a further aspect the invention provides an FcR allele-specific binder for use in a method of prognosis, prophylaxis or therapy according to the invention.

Viewed from a still further aspect, the invention provides the use of a material prophylactically or therapeutically effective against a disease selected from multiple sclerosis, myasthenia gravis, diabetes mellitus, cerebrovascular and cardiovascular diseases, atherosclerosis, and Addison's disease for the

addition to this variety, certain FcγR genes have allelic variants which affect their receptor function.

Thus for example FcγRIIA is expressed on monocytes, macrophages and neutrophils and has several allelic forms leading to FcγRIIA polymorphism. One variant contains histidine (131 H) while another contains arginine (131 R). The H/H variant has higher affinity for IgG2 than the R/R variant. Similarly, FcγRIIIB, which is only expressed on neutrophils, has several allelic forms with individuals homozygous for FcγRIIIB neutrophil antigen (NA)1 being more efficient in binding IgG1 and IgG3 than individuals homozygous for the NA2 allele. FcγRIIA and FcγRIIIB can also be simultaneously ligated leading to collaboration in the initiation of integrated cell functions.

The FcR genotype identified according to the invention is preferably FcγRIIIB and/or FcγRIIA, although more preferably both are identified. Nevertheless, the invention may be performed using other FcR genes which show allelic variation, especially FcR which are expressed on macrophage, neutrophil, microglia, endothelial cell or foam cell surfaces.

It must be emphasized here that the individual FcR genotype is not primarily being suggested as a marker for presence of or susceptibility to the selected disease, ie. whether or not the individual has a higher or lower than average likelihood of contracting the disease. Instead, identification of the FcR genotype according to the invention allows a prediction to be made of the severity and course of the disease should the individual contract it, or already have contracted it. Genetic markers (e.g. in the MHC region) for susceptibility to autoimmune and immune-related diseases are known, and in a further aspect the present invention provides a method of disease prognosis for a disease selected from multiple sclerosis, myasthenia gravis, diabetes mellitus, cerebrovascular and cardiovascular

diseases, atherosclerosis, and Addison's disease, which method comprises determining the presence or absence of a genetic marker for susceptibility to said disease in the DNA of a human or non-human animal subject and determining the genotype of said subject for at least one Fc receptor, preferably an Fcγ receptor, and identifying whether the determined genotype corresponds to a benign or non-benign prognosis for said disease, said method optionally also involving carrying out a diagnostic imaging procedure on said subject, carrying out surgical intervention on said subject, or administering a prophylactally or therapeutically effective amount of a material prophylactally or therapeutically effective against said disease to said subject where said marker is present and said genotype corresponds to a non-benign prognosis. In further aspects, the invention provides prognostic kits and the use of FcR allele-specific binders and of therapeutic and prophylactic materials for the manufacture of compositions for use in such a method.

Viewed from a further aspect the invention provides a diagnostic assay for a disease selected from multiple sclerosis, myasthenia gravis, diabetes mellitus, cerebrovascular and cardiovascular diseases, atherosclerosis, and Addison's disease, said assay comprising obtaining a sample of DNA from a human or non-human mammal subject (e.g. involving separating such a sample deriving from a body fluid such as blood); and identifying the genotype of that DNA for a Fc receptor (preferably an FcγRIIA and an FcγRIIIB), for example by amplifying a segment of that DNA containing at least a characteristic part of the gene for that receptor and identifying the allele or alleles of the gene for that receptor present in that DNA; and optionally identifying the presence or absence in that DNA of a genetic marker for susceptibility to the selected disease, e.g. an MHC region marker for susceptibility to multiple sclerosis.

Claims

1. A method of disease prognosis which involves determining the genotype of a human or non-human mammal subject for at least one Fc receptor, and identifying whether the determined genotype corresponds to a benign or non-benign prognosis for a disease selected from multiple sclerosis, myasthenia gravis, diabetes mellitus, cerebrovascular and cardiovascular diseases, atherosclerosis, and Addison's disease.

2. A method of prophylaxis or therapy of a human or non-human mammal subject to combat a disease selected from multiple sclerosis, myasthenia gravis, diabetes mellitus, cerebrovascular and cardiovascular diseases, atherosclerosis, and Addison's disease which method comprises determining the genotype of said subject for at least one Fc receptor, identifying whether the determined genotype corresponds to a benign or non-benign prognosis for said disease, and, where said determined genotype corresponds to a non-benign prognosis, carrying out a diagnostic imaging procedure on said subject, carrying out surgical intervention on said subject, or administering a prophylactically or therapeutically effective amount of a material prophylactically or therapeutically effective against said disease to said subject.

3. A method of disease prognosis for a disease selected from multiple sclerosis, myasthenia gravis, diabetes mellitus, cerebrovascular and cardiovascular diseases, atherosclerosis, and Addison's disease which comprises determining the presence or absence of a genetic marker for susceptibility to said disease in the DNA of a human or non-human animal subject and determining the genotype of said subject for at least one Fc receptor, and identifying whether the determined

genotype corresponds to a benign or non-benign prognosis for said selected disease.

4. A method as claimed in claim 3 also involving administering a prophylactally or therapeutically effective amount of a material prophylactally or therapeutically effective against said selected disease to said subject where said marker is present and said genotype corresponds to a non-benign prognosis.

5. A diagnostic assay comprising obtaining a sample of DNA from a human or non-human mammal subject and identifying the genotype of that DNA for a Fc receptor and optionally identifying the presence or absence in that DNA of a genetic marker for susceptibility to a disease selected from multiple sclerosis, myasthenia gravis, diabetes mellitus, cerebrovascular and cardiovascular diseases, atherosclerosis, and Addison's disease.

6. The use of an FcR allele-specific binder for the manufacture of a composition for use in a method of prognosis, prophylaxis or therapy as claimed in any one of claims 1 to 4.

7. A method, use or a diagnostic assay as claimed in any one of claims 1 to 6 wherein said Fc receptor is an Fcγ receptor.

9. A method, use or a diagnostic assay as claimed in claim 7 wherein said Fcγ receptor is Fcγ RIIA and/or Fcγ RIIIB.

9. A method, use or diagnostic assay as claimed in any one of claims 1 to 8 wherein for multiple sclerosis FcγRIIIB NA1/NA1 and FcγRIIA H/H, together or separately are indicative of a benign prognosis.

10. A method, use or diagnostic assay as claimed in any one of claims 1 to 8 wherein for myasthenia gravis FcγRIIIB NA1/NA1 is indicative of a non-benign prognosis and R/R + NA2/NA2 is indicative of a benign prognosis.

11. A method, use or diagnostic assay as claimed in any one of claims 1 to 8 wherein for diabetes mellitus FcγRIIIB NA1/NA1 and/or FcγRIIA H/H is indicative of a non-benign prognosis.

12. A method, use or diagnostic assay as claimed in any one of claims 1 to 8 where for atherosclerosis and cardiovascular or cerebrovascular disease FcγRIIIB NA2/NA2 is indicative of a non-benign prognosis.

13. A method, use or diagnostic assay as claimed in any one of claims 1 to 8 wherein for Addison's disease FcγRIIA H/H is indicative of a non-benign prognosis.

14. A prognostic kit comprising at least one FcR allele-specific binder and instructions for the performance of a method of prognosis, prophylaxis or therapy as claimed in any one of claims 1 to 4 and 7 to 13.

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(71) Applicant *(for all designated States except US)*: STIFTELSEN UNIVERSITETSFORSKNING BERGEN (UNIFOB) [NO/NO]; UNIFOB, N–5020 Bergen (NO).

(71) Applicant *(for GB only)*: COCKBAIN, Julian [GB/GB]; 102 Cranbrook Road, London W4 2L5 (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: NYLAND, Harold, Inge [NO/NO]; University of Bergen, Dept. of Neurology, Haukeland Hospital, N–5021 Bergen (NO). MYHR, Kjell–Morten [NO/NO]; University of Bergen, Dept. of Neurology, Haukeland Hospital, N–5021 Bergen (NO). VEDELER, Christian, Alexander [NO/NO]; University of Bergen, Dept. of Neurology, Haukeland Hospital, N–5021 Bergen (NO).

(74) Agents: COCKBAIN, Julian et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

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A method of disease prognosis which involves determining the genotype of a human or non–human mammal subject for at least one Fc receptor, and identifiying whether the determined genotype corresponds to a benign or non–benign prognosis for a disease selected from multiple sclerosis, myasthenia gravis, diabetes mellitus, cerebrovascular and cardiovascular diseases, atherosclerosis, and Addison's disease.

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